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"On the Coagulation of the Blood." Preliminary Communication.

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The theory to account for the coagulation of the blood which is most generally accepted at the present day is that of Hammarsten; he teaches that coagulation is dependent upon the conversion of a proteid substance, fibrinogen, which exists in solution in the plasma, into fibrin by means of a ferment liberated by the disintegration of the white blood corpuscles which occurs when the blood leaves the living blood-vessels. This theory has replaced the older one of Al. Schmidt, who taught that fibrin is formed by the union of two fibrin-generators, one of which is the fibrinogen just mentioned, and the other of which he called fibrinoplastic substance or paraglobulin; this union, moreover, occurs under the influence of a third factor, the fibrin ferment.* Hammarsten† showed that paraglobulin, or as it is now more generally called serum globulin, is not necessary for the formation of fibrin.

The present research was directed to determining the nature of the ferment that produces this change in fibrinogen. The result at which I have arrived is sufficiently definite to warrant a preliminary statement of the facts observed; the full details of the experiments, as well as those of certain others which are at present in progress, will be reserved for a later communication.

I will first briefly relate some preliminary experiments‡ which had

* 'Pflüger's Archiv,' vol. 6, p. 413 *et seq.*

† *Ibid.*, vol. 14, p. 211; 17, p. 413; 18, p. 38; 19, p. 563.

‡ An account of some of these preliminary experiments is contained in the report

for their object a separation and recognition of the various proteids contained in lymph cells. An animal (generally a cat) was chloroformed and killed by bleeding from the carotids; the thorax was quickly opened, and a cannula inserted in the aorta; a stream of salt solution ($\frac{3}{4}$ per cent.) at considerable pressure was passed through the vessels by this means, in about a minute the large veins entering the heart were opened and the mixture of blood and saline solution allowed to escape. When the fluid came through perfectly colourless, the abdominal glands were removed, freed from their capsules, cut into small pieces, and ground up in a mortar with saline solution; any portions of the gland capsules which still remained were removed, and the fluid with the cells suspended in it was poured into test-tubes, the cells settled, and the process of settling was hastened by centrifugalising, the supernatant liquid was poured off, and the cells again washed with saline solution in the same way. By this method the cells were quickly freed from any lymph that might still have been in contact with them.

Microscopical examination showed that they still possessed their normal appearances, except for a small amount of shrinkage. The supernatant saline liquid was found to contain in small quantities the proteids which were afterwards found in the cells, a certain amount of their proteid constituents having thus entered into solution.

The liquid which was found best for dissolving the proteids of the lymph cells thus obtained was prepared by mixing a saturated solution of magnesium sulphate with nine times its volume of distilled water; and the proteids present in such an extract were as follows:—

1. A mucin-like proteid similar to that described by Miescher* in pus which swells up into a jelly-like substance when mixed with solutions of sodium chloride or magnesium sulphate.
2. Two globulins.
3. An albumin.

It will be convenient to take these proteids one by one, and describe the chief properties of each.

1. *The Mucin-like Proteid.*—If the cells are extracted with a 5 per cent. sodium chloride or magnesium sulphate solution, the result is a slimy mass, resembling mucus in appearance. The proteid which causes this appearance may be obtained pure by pouring this mixture into a large excess of distilled water; this peculiar proteid then extends in cohesive strings throughout the water, which in time contract and float on the top, and may be then thoroughly washed with distilled water. The following are its chief properties; it is insoluble in water, slightly soluble in $\frac{3}{4}$ per cent. saline solution, as shown by

of a committee appointed by the British Association to investigate the physiology of the lymphatic system ('Brit. Assoc. Rep.,' 1887, p. 145).

* Hoppe-Seyler's 'Med. Chem. Untersuchungen,' p. 441.

the fact that such a solution becomes slimy when the proportion of salt is increased to 5 per cent. It is also slightly soluble in the sodium sulphate solution used. When this proteid is suspended in water or salt solution the mucus-like strings shrink at about 50° C., and can be easily filtered off. In the case of sodium sulphate extracts of the glands, it is apparently carried down with the globulin that coagulates at that temperature. Saturation with neutral salts, sodium chloride, magnesium sulphate, and especially ammonium sulphate, causes also shrinkage of the swollen masses, and renders filtration easier. It is precipitable by absolute alcohol, basic lead acetate, and by solution of tannin. It is precipitated by acetic acid in strings like mucin; like mucin also it is soluble in baryta or lime-water, from which solution it is again precipitable by acetic acid, and only soluble in considerable excess of that reagent.

This substance, however, is not mucin, as prolonged boiling with sulphuric acid does not cause it to yield any reducing sugar. It is also not nuclein of which the cell nuclei are made up, as the nuclei are not attacked by such reagents as $\frac{3}{4}$ per cent. sodium chloride in which this substance is slightly soluble. It, however, like nuclein, yields an ash which is rich in phosphorus; it dissolves in 0·2 per cent. hydrochloric acid, and on adding pepsin to this solution an insoluble residue rich in phosphorus separates out. Otherwise this substance has the nature of a globulin, but one which is much more readily precipitated by neutral salts than most globulins are; a proportion of 5 per cent. of sodium chloride for instance in its solutions rendering it insoluble; but the precipitate so produced is not of the usual fine flocculent character, but a slimy mucus-like one. In all these points this proteid resembles in its characters a class of proteids which have been recently named "nucleo-albumins" by Hammarsten.* He has separated these mucin-like globulins from the bile, and from synovial fluid where they have long been mistaken for mucin, and from the cells of the submaxillary gland, which contain, however, true mucin in addition.

2. *The Globulins.*—There is a small quantity of a globulin which enters into the condition of a heat coagulum at about 50° C. The most abundant globulin is, however, one which resembles serum globulin in its heat coagulation temperature (75° C.), and in the way in which it is precipitated by saturation with salts, or by dialysing out the salts from its solutions.

The term serum globulin is hardly applicable to a proteid existing in lymph cells; hence it is necessary to multiply terms, and to designate this globulin by a new name, viz., *cell globulin*. It has, moreover, certain characteristic properties which will be fully dealt with later on.

* 'Zeitschr. Physiol. Chem.,' vol. 12, p. 163.

3. *The Albumin* resembles serum albumin in its properties. It coagulates at 73° C. It is present in very small quantities. It may be provisionally termed *cell albumin.*

In concluding this account of the proteids of lymph cells, I may add that no substance like myosin or fibrin can be obtained from the cells; there is, however, a formation of sarkolactic acid after death as in muscle; and if the glands be left, especially at the temperature of the body, for some hours after death, a process of self-digestion takes place, the pepsin present in the glands as it is in most tissues (Brücke) becoming active when the reaction of the tissue becomes acid; under these circumstances there is in addition to the proteids already enumerated a small and varying amount of albumoses and peptones.

Having thus recognised the various proteids that occur in the cells of lymphatic glands, my next endeavour was to ascertain what action, if any, these exerted on the coagulation of the blood. My experiments in this direction have been mostly performed with salted plasma. The blood is received into an approximately equal volume of saturated sodium sulphate solution. By this means coagulation is prevented, and the corpuscles settle. On subsequently removing the supernatant salted plasma, and diluting it with four or five times its bulk of water, coagulation occurs after the lapse usually of several hours; but if, instead of water, a solution of fibrin ferment be used, coagulation occurs in a few minutes.

I first tried to prepare fibrin ferment from the lymphatic glands; these were freed from blood, chopped small, and placed under absolute alcohol for some months; they were then dried over sulphuric acid, powdered, and the dry powder extracted with water. The water was found to contain the fibrin ferment. It hastened very considerably the coagulation of salted plasma. This activity was destroyed at a temperature between 74° C. and 80° C. The watery extract gave, moreover, the xanthoproteic reaction; it contained also some sodium chloride and phosphates which it had dissolved out of the dried glands.

A watery or saline extract of fresh glands also had very considerable clotting powers;* that is to say, the addition of a few drops of such an extract caused diluted salted plasma to clot in a few minutes, which otherwise did not clot until after the lapse of 12—24 hours. The activity of this extract was not altered by heating to 70°; it was therefore independent of the nucleo-albumin which is disintegrated at about 50° C., or of the globulin which coagulates at that temperature. Its activity was destroyed, however, if heated above 75° C. These facts show that the extracts of both dried and fresh glands contain a substance which has the same properties as fibrin ferment,

* I find that this fact has been previously noted by Rauschenbach, 'Inaug.-Dissert.,' Dorpat, 1882, p. 26.

and which, moreover, is rendered inactive at the temperature at which fibrin ferment, as ordinarily prepared from serum, loses its activity.

The next question which I investigated was whether the ferment action was dependent upon, or independent of, the presence of the proteids of the cells. An extract of the cells was made with sodium sulphate solution, and saturated with ammonium sulphate; the precipitate of the proteids so produced was filtered off; the proteid-free filtrate dialysed till free from excess of salt,* and it was then found to have no power of hastening coagulation. The precipitate which contained all the proteids was washed by saturated solution of ammonium sulphate, and redissolved by adding distilled water (Solution A); this solution hastened the coagulation of salted plasma very considerably. This experiment showed either that the ferment was identical with or precipitated with the proteids in the extract. It was, moreover, destroyed at a temperature at which these proteids were coagulated, viz., about 75° C.; there are, however, in Solution A two proteids which are coagulated at about this temperature, viz., the cell globulin and the cell albumin. These were separated by saturating the solution with magnesium sulphate; the globulin was precipitated, washed, and redissolved by adding water (Solution B). The filtrate from this precipitate was dialysed till free from salt (Solution C). Solution B was dialysed until nearly free from salt, but not sufficiently free to cause precipitation of the globulin; it was divided into two equal parts, B′ and B″; B′ underwent no further treatment. B″ was dialysed till the globulin was precipitated; the globulin was then filtered off, washed with distilled water, the precipitate dissolved in 0·3 per cent. sodium chloride solution (Solution D). The solution B″ *minus* the globulin precipitated by dialysis still contained a small quantity of globulin; this may be called Solution E.

The influence of each of these solutions on dilute salted plasma was then investigated. The results may be summarised as follows:—

Solution C (containing only cell albumin) did not hasten the coagulation of salted plasma, but in some cases even caused delay.

Solution B′ (containing only cell globulin) hastened very considerably the coagulation of such plasma.

Solution E (containing very little cell globulin) hastened the coagulation to a slight extent.

Solution D (containing the cell globulin precipitated from Solution B by dialysis) hastened the coagulation considerably.

These experiments show that it is not the albumin but the globulin

* This experiment, and the others in which dialysis was employed, were carried out in the cold winter months, and thymol was always added to prevent putrefaction.

which has the properties of fibrin ferment. It might be urged that the ferment is not identical with the globulin, but is only closely associated with it. Such an objection seems to me to be a mere splitting of hairs. If the ferment is so closely associated with the globulin that none of the methods used of preparing the globulin pure are capable of separating it from the ferment, and if, moreover, the activity of the ferment is destroyed when the distinctive characters of the globulin are destroyed, as by heating to 75° C., then we are not justified in saying that the globulin is different from the ferment, until some method is shown by which they may be separated.

After I had performed the experiments just related, the question naturally arose, is this cell globulin the same thing as what has been termed fibrin ferment when prepared from serum? The experiments that I performed in attempting to find an answer to this question were as follows:—

A large quantity of cat's serum was taken, and to it was added 10 to 15 times its volume of absolute alcohol. The resulting precipitate was allowed to stand under the alcohol for about three months; the alcohol was then filtered off, and the precipitate dried over sulphuric acid and powdered. On extracting this powder with water, especially with warm water, a very active preparation of fibrin ferment was obtained. Like all preparations of the fibrin ferment, it gave the xanthoproteic reaction, but sufficient proteid was not present to enable one to identify it. The extract was therefore concentrated at 40° C.; it was then found to contain a proteid which was coagulated by heat at 75° C. It was precipitated by dialysing out the salts from its solutions, and it was also precipitated by saturation with magnesium sulphate;* the precipitate produced by magnesium sulphate was collected, washed with a saturated solution of magnesium sulphate, and redissolved by the addition of water, the adherent salt rendering it soluble. This solution has very marked ferment properties; it hastened the coagulation of salted plasma; it caused pericardial fluid to clot rapidly; and it also hastened the coagulation of pure plasma obtained from the jugular vein of the horse. This last-mentioned experiment is of especial importance, as here the plasma was unmixed with any foreign substance. The jugular vein of a horse was removed after being ligatured in two places to prevent the blood escaping; the "living test-tube" was suspended in a cold place over night, and in the morning the corpuscles had subsided; the plasma above these was almost free from corpuscles; and when removed from top of the vein by a pipette did not clot for about half an hour at the temperature of the air (11° C.); but a similar portion to which a few drops of

* After filtering off the precipitate produced by magnesium sulphate, the filtrate contained the merest trace of proteid, and on dialysing away the excess of salt, it was found to have lost all the properties of fibrin ferment.

the ferment globulin had been added coagulated in about two minutes.

The question will be asked, how is it if the ferment is a globulin it can be extracted by means of distilled water from the ferment powder? The answer to that question is that the water is enabled to dissolve the globulin by a portion of the salts, especially sodium chloride, in the ferment powder entering into solution at the same time. That this is the correct answer was shown by the following experiment:—A quantity of the ferment powder was subjected to prolonged washing with warm (40° C.) distilled water; it was then suspended in water, and dialysed for three weeks, thymol being added to prevent decomposition. At the end of this time it was dried over sulphuric acid; it was then found that warm water was able to extract only the faintest trace of proteid from the powder, and that this extract had little or no ferment action, while an extract of the same powder with a 0·3 per cent. sodium chloride solution contained much more proteid and had powerful ferment properties.

Serum globulin prepared from sheep's and horse's serum by repeated precipitation with magnesium sulphate, and finally by dialysis, was found to possess powerful ferment properties; this entirely confirms Al. Schmidt's statement that he has been unable to prepare from serum "fibrinoplastic substance" free from ferment.* This is easily explained when one considers that serum globulin as prepared from serum contains a certain admixture of cell globulin derived from the disintegration of white blood corpuscles; and this is precipitated with the globulin which pre-existed in the blood plasma. On the other hand, serum globulin prepared from a liquid like hydrocele fluid which does not coagulate spontaneously, has no such ferment properties. This confirms Hammarsten's statement that he has obtained from hydrocele fluid a pure paraglobulin free from ferment, and which exerted no fibrinoplastic activity.

I will here quote a typical experiment which brings out the fibrinoplastic properties of globulin prepared from serum, and the absence of such properties in the globulin prepared from hydrocele fluid:—

Ox sodium sulphate plasma was diluted with four times its volume of liquid in each of the succeeding experiments; the diluted plasma was then divided into two parts, one part was kept at the temperature of the air (14° C.), the other at the temperature of 40° C. in an incubator.

Thus the plasma which was diluted with a saline solution of globulin from hydrocele fluid, coagulated at approximately the same time as that in which the saline solution alone was employed as the diluent,

* I have also confirmed Schmidt's statement that serum globulin (Schmidt's fibrinoplastic substance) which is precipitated by a stream of carbonic acid, has ferment properties.

Dilution with	Coagulation occurred	
	At 14° C.	At 40° C.
1. 0·3 per cent. NaCl solution.....	In 46 minutes	In 20 minutes.
2. Globulin from horse serum dissolved 0·3 per cent. NaCl solution.....	„ 10 „	„ 2 „
3. Globulin from hydrocele fluid in 0·3 per cent. NaCl solution	„ 47 „	„ 22 „

while a specimen diluted with a saline solution of globulin from serum coagulated in about one-fifth of that time. The explanation of this difference in the action of the serum globulin as derived from these two sources is perfectly clear in the light of the foregoing researches in the ferment powers of cell globulin.

The serum globulin from hydrocele fluid contains no ferment, because it contains pure serum globulin and no cell globulin.

The serum globulin obtained from serum contains in addition to the serum globulin that existed in the blood plasma, a certain quantity of cell globulin formed by the disintegration of white corpuscles.

Both Schmidt and Hammarsten have recognised the fact that the amount of globulin in the serum was greater than in the plasma, and that this extra amount was derived from the white blood corpuscles. The object of this paper is to point out that this extra globulin derived from the white corpuscles is in reality fibrin ferment. I may here mention that examination of the ash of this substance shows that it contains no phosphorus.

Preparations of serum from which the globulin had been removed by saturation with magnesium sulphate, and the excess of salt by dialysis, were found to have no ferment activity at all. Schmidt found that serum *minus* its globulin (precipitated by a stream of carbonic anhydride) has very little ferment activity; the explanation of its still possessing any is that carbonic acid does not completely precipitate the globulin. When, however, the globulin is completely removed by magnesium sulphate, all ferment activity is completely removed also.

An extract of "washed blood clot" was found by Buchanan* to hasten the formation of fibrin. Gamgee,† on repeating Buchanan's experiments, concluded that the substance in saline extracts of fibrin which had the powers of fibrin ferment was a globulin; and this view entirely coincides with the conclusions I have arrived at. In a few experiments in which I have used a 5 per cent. magnesium sulphate extract of fibrin, I obtained in the extract a globulin which has all

* 'London Medical Gazette,' vol. 18, p. 50.

† 'Journal of Physiology,' 1879.

the properties of fibrin ferment, which coagulates at 75° C., and agrees in all other particulars with the substance I have named cell globulin. It is derived doubtless from the white corpuscles entangled in the clot. Lea and Green,* who repeated Gamgee's experiments, came to somewhat opposite conclusions; they, however, never obtained the ferment free from proteid, but they concluded it was not a globulin as it was soluble in distilled water; they admitted, however, that it was much more soluble in saline solutions; reading these experiments in the light of a more recent paper by one of them,† it is evident that they were dealing in large measure with calcium sulphate, a salt which has considerable powers of aiding the activity of the fibrin ferment.

The final conclusions that are to be drawn from these researches are as follows:—

1. Lymph cells yield as one of their disintegration products a globulin which may be called cell globulin. This has the properties that have hitherto been ascribed to fibrin ferment.

2. Fibrin ferment as extracted from the dried alcoholic precipitate of blood serum is found on concentration to be a globulin with the properties of cell globulin.

3. The fibrin ferment as extracted by saline solutions from "washed blood clot" is a globulin which is also identical with cell globulin.

4. Serum globulin as prepared from hydrocele fluid has no fibrinoplastic properties. It may perhaps better be termed plasma globulin.

5. Serum globulin as prepared from serum has marked fibrinoplastic properties. This is because it consists of plasma globulin, and cell globulin derived from the disintegration of white blood corpuscles, which are in origin lymph cells.

6. The cause of the coagulation of the blood is primarily the disintegration of the white blood corpuscles; they liberate cell globulin which acts as a ferment converting fibrinogen into fibrin. It does not apparently become a constituent part of the fibrin formed.

This confirmation and amplification of Hammarsten's views concerning the cause of the coagulation of the blood is in direct opposition to the theories of Wooldridge. My methods have not been the same as those adopted by Wooldridge, but the final conclusions are so different, that it is necessary I should state my reasons for not accepting his views, nor adopting his methods. Wooldridge's theory may be stated as follows:‡—The coagulation of the blood is a phenomenon essentially similar to crystallisation; in the plasma there are three constituents concerned in coagulation, A, B, and C fibrinogen.

* 'Journ. of Physiol.,' vol. 4, p. 380.

† Green, 'Journ. of Physiol.,' vol. 8, p. 355.

‡ Croonian Lecture, Royal Society, 1886.

A and B fibrinogen are compounds of lecithin and proteid, and fibrin results from the transference of the lecithin from A fibrinogen to B fibrinogen. C fibrinogen is what has hitherto been called fibrinogen; A fibrinogen is a substance which may be precipitated by cooling "peptone plasma," and on the removal of this substance coagulation occurs with great difficulty. The precipitate produced by cold consists of rounded bodies resembling the blood-plates in appearance. He further found that other compounds of lecithin and proteid to which he has extended the name of fibrinogen exist in the testis, thymus, and other organs, in the fluid of lymph glands, and in the stromata of red corpuscles; these substances may be extracted from the organs by water, and precipitated from the aqueous extract by acetic acid, and on redissolving this in a saline solution, and injecting it into the circulation of a living animal, intravascular clotting occurs which results in the death of the animal. This form of fibrinogen (?) that acts thus he looks upon as the precursor of A fibrinogen. From these points of view the fibrin ferment and the white corpuscles are looked upon as of secondary import in causing coagulation, though it is admitted that fibrin ferment converts C fibrinogen into fibrin.

In a more recent paper* these fibrinogens are somewhat differently lettered; B fibrinogen seems to have disappeared, and C fibrinogen now receives that name.

I have been carefully through all Wooldridge's papers, and I have by examination of the statements made therein, and by a few test experiments of my own, come to the conclusion that the theory is untenable; I will take up the chief facts upon which the theory rests, one by one.

1. *The Influence of Lecithin in the Coagulation of the Blood.*—Lecithin hastens the coagulation of blood-plasma, which has been prevented from clotting by the injection into the circulation of a certain quantity of commercial peptone.† The term "peptone plasma" is a convenient one to retain, though it must be remembered that it is not the peptone in it that has the action in question, but the albumoses, and especially heteroalbumose.‡ Wooldridge§ also found by receiving the blood of a dog into a thick emulsion of lecithin coagulation occurred more quickly than when it was received into a corresponding quantity of saline solution.

It is upon these experiments that the theory that lecithin is the essential cause of the coagulation depends. I am very little inclined

* Ludwig's 'Festschrift,' p. 221.

† Wooldridge, 'Journ. of Physiol.,' vol. 4, p. 226.

‡ Pollitzer, 'Journ. of Physiol.,' vol. 7, p. 289. Pollitzer also found that these proteids also delayed the coagulation of blood after it was shed. I have found them to cause a similar delay in the clotting of dilute salted plasma.

§ 'Journ. of Physiol.,' vol. 4, p. 367.

to place reliance on the experiments on dog's blood just quoted, as he finds it necessary to use an emulsion as thick as milk to produce the effect, and it is well known that contact with any foreign matter, especially if it is finely divided, will hasten coagulation, and it cannot be supposed that sufficient lecithin is normally concerned in forming fibrin as to cause a thick emulsion like this. Moreover, addition of lecithin does not cause the clotting of pericardial fluid, of hydrocele fluid, of solutions of fibrinogen,* of dilute salted plasma,† and I am not aware that it has been tried on pure plasma obtained by the living test-tube experiment. It then simply hastens the coagulation of peptone plasma, and peptone plasma, as I shall show more fully in the next section, differs so much from normal plasma, that it is impossible to draw correct conclusions from experiments performed with it, unless they be supported by confirmatory evidence on solutions of fibrinogen and pure plasma, such as one obtains from a vein, or from the pericardial sac.

The solutions of lecithin used were admittedly impure,‡ and it is possible that there was present a certain amount of calcium sulphate, even if there was no fibrin ferment. But supposing it was the lecithin and not the impurities that hastened the coagulation in question, it must be remembered that many other organic and inorganic substances act similarly; thus Nauck§ has shown that small quantities of glycin, uric acid, &c., as well as lecithin hasten coagulation, and Green‖ that calcium sulphate does so also. But it is not concluded from these observations that these are the chief agents in bringing about the coagulation of the blood. I have found that cell globulin contains no phosphorus, and Wooldridge admits¶ that Schmidt's ferment is free from lecithin. On the very same page, however, he accounts for the loss of the activity of fibrin ferment, which was observed to take place by Hammarsten when it was kept long under alcohol, as being due to removal of lecithin.**

The supposition that "fibrinogen A" acts by giving up its lecithin to "fibrinogen B" to form fibrin, seems, therefore, to be a pure assumption, and so far as I can find is unsupported by any analytical evidence. Wooldridge has certainly shown that the fibrinogens (?) he obtains from tissues contain phosphorus, but to this point I shall return later.

* 'Journ. of Physiol.,' vol. 4, p. 369.

† Private communication to the author.

‡ 'Journ. of Physiol.,' vol. 4, p. 369.

§ 'Inaug.-Dissert.,' Dorpat, 1886.

‖ *Loc. cit.*

¶ 'Journ. of Physiol.,' p. 230.

** This loss of activity is well explained by my theory, by supposing that the longer cell globulin is kept under alcohol, the more insoluble in water does it become, like all other proteids.

2. *The Precipitate produced by cooling Peptone Plasma* (Wooldridge's fibrinogen A).—The occurrence of this precipitate is evidently regarded by Wooldridge as one of the most important facts upon which his theory is founded. Here, again, I am willing to concede the fact observed, but differ from Wooldridge with regard to its interpretation. The chief point I wish to urge is that this precipitate is obtained on cooling peptone plasma only, and from no other form of plasma. I have repeatedly attempted to obtain such a precipitate by cooling to 0° C. pure plasma from the veins of the horse,* salted plasma, prepared by mixing blood with various proportions of different salts, hydrocele fluid, and pericardial fluid, but in all cases with a negative result. It, therefore, occurs in peptone plasma alone; and that it is due to the peptone is supported by the fact that if one takes an aqueous solution of "Witte's peptone" and cools it to 0° C., a precipitate is formed consisting of rounded granules, which were mistaken under the microscope by several friends in the laboratory for blood-tablets. I, moreover, found that this precipitate consists of heteroalbumose, and when that substance (which as Neumeister† has shown is more soluble in water than has been hitherto supposed) has been removed by dialysis and filtration, the remaining albumoses and peptones are not precipitated by cold. The precipitate of heteroalbumose, which is obtained by dialysis of saline solutions of "Witte's peptone," also consists of similar rounded granules.

Peptone plasma, it may be said, does not contain peptone or albumoses; or rather that it is difficult to discover them in "peptonised blood." It is undoubtedly difficult, because they are present in such small proportion that they are obscured by the overwhelmingly large amount of globulin and albumin present. But as Neumeister‡ has shown that they are, after injection into the circulation, excreted by the kidneys, we must also conclude that they exist as such for a time in the blood.

How their presence there prevents coagulation it is difficult to say; it is possible that they may cause by their presence a change in the normal proteids of the blood that prevents the formation of or the action of the fibrin ferment. That peptone blood does differ in one other important particular from normal blood, viz., in the heat coagulation temperatures of its proteids, was shown by Wooldridge

* I have found that if the plasma is completely frozen, that on subsequently thawing it, coagulation sets in very quickly (in 10—20 seconds); this is probably due to the crystals of ice breaking up the white corpuscles, many of which still float in the plasma. Nauck also has noted this and gives a similar explanation (*loc. cit.*, p. 20). After removing these by centrifugalising for two hours in vessels surrounded by ice, no such phenomenon occurs, and clotting does not set in for fully fifteen minutes after thawing.

† 'Zeitschr. Biol.,' vol. 24, p. 269.

‡ *Ibid.*, vol. 24, p. 281 *et seq.*

himself.* It is on these grounds, then, that I hold we cannot regard peptone plasma as being at all comparable to normal plasma.

With the removal of "fibrinogen A" the whole complex theory as formulated by Wooldridge falls to the ground; and we are left with "fibrinogen B" of the later communication, which is Hammarsten's fibrinogen. It is advisable to confine strictly the use of the term "fibrinogen" to this substance.

3. *Intravascular Coagulation.*—Under this heading my remarks will be of the nature of criticism only. No doubt the crude and impure substance (for there is no attempt at purification, separation, or identification) introduced into the veins produces intravascular clotting; but I must protest against the extension of the name fibrinogen to such substances. It seems to me it would be just as correct to call a piece of iron wire introduced into the sac of an aneurysm to produce coagulation there, a fibrinogen.

Some of Wooldridge's experiments under this head have been repeated by Krüger;† he finds, in opposition to Wooldridge, that leucocytes themselves produce intravascular clotting (which would agree perfectly well with the cell globulin theory), and also that the stromata of red corpuscles, which probably contain the same constituents in great measure as the white corpuscles, act similarly; other experiments have led him to the conclusion that it is the corpuscular elements that play the chief part in the coagulation, both within and without the body. He entirely negatives the statement of Wooldridge that the fluid of the lymph gland produces this effect, and any slight action it may have is accounted for by the presence of some leucocytes, which are exceedingly difficult to remove completely, even by centrifugalising.

To return, however, to these tissue fibrinogens of Wooldridge, I think we may venture to offer a suggestion as to their real nature, or, at any rate, as to the nature of one of their constituents. From the last paper published by Wooldridge,‡ we find that they are imperfectly soluble in water, readily precipitated by acids, and soluble in excess of those reagents. That they yield on gastric digestion a substance which is insoluble and which is rich in phosphorus. From these details of their properties, I think, we may draw the conclusion not that they contain lecithin, as Wooldridge affirms, but that they belong to the group of proteids described in the former part of this paper under Hammarsten's name of nucleo-albumin. Nucleo-albumins yield when poured into water a stringy precipitate resembling mucin, and in a former paper Wooldridge§ speaks of the preci-

* 'Roy. Soc. Proc.,' vol. 38, 1885, p. 263.
† 'Zeitschr. Biol.,' vol. 24, p. 189 *et seq.*
‡ 'Roy. Soc. Proc.,' vol. 43, 1888, p. 367.
§ *Ibid.*, vol. 40, 1886, p. 134.

pitate of his tissue fibrinogen (precipitated by acetic acid) as being a bulky one. If my conjecture is correct, it would be exceedingly likely that when a saline solution of such a substance was injected into the circulation, it would form strings of a slimy mucinoid description in the vessels, and that these would form the starting-point for the thrombosis or intravascular coagulation that ensues.

June 7, 1888.

The Annual Meeting for the Election of Fellows was held this day.

Professor G. G. STOKES, D.C.L., President, in the Chair.

The Statutes relating to the election of Fellows having been read, Sir William Bowman and Dr. Gladstone were, with the consent of the Society, nominated Scrutators to assist the Secretaries in examining the lists.

The votes of the Fellows present were then collected, and the following candidates were declared duly elected into the Society :—

Andrews, Thomas, F.R.S.E.
Bottomley, James Thomson, M.A.
Boys, Charles Vernon.
Church, Arthur Herbert, M.A.
Greenhill, Professor Alfred George, M.A.
Jervois, Sir William Francis Drummond, Lieut.-Gen. R.E.
Lapworth, Professor Charles, LL.D.
Parker, Professor T. Jeffery.
Poynting, Professor John Henry, M.A.
Ramsay, Professor William, Ph.D.
Teale, Thomas Pridgin, F.R.C.S.
Topley, William, F.G.S.
Trimen, Henry, M.B.
Ward, Professor Henry Marshall, M.A.
White, William Henry, M.I.C.E.

Re-elected.

Clarke, Alexander Ross, Colonel R.E.

Thanks were given to the Scrutators.